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PATENT  
Docket No. 220002057202  
Client Ref. No. 1995-091-4



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In the application of:

Wolfgang H. DILLMANN et al.

Serial No.: 09/664,127

Filing Date: September 18, 2000

For: GENE THERAPY FOR MYOCARDIAL  
ISCHEMIA

Examiner: S. Chen

Group Art Unit: 1633

DECLARATION OF DR. WOLFGANG H. DILLMANN  
PURSUANT TO 37 C.F.R. § 1.132

Assistant Commissioner for Patents  
Washington, D.C. 20231

Dear Sir:

I, Dr. Wolfgang H. Dillmann, declare as follows:

1. I am currently a Professor of Medicine at the University of California at San Diego. I am an expert in the area of Endocrinology and pathophysiological basis of cardiovascular disease. A current copy of my Curriculum Vitae is attached hereto as Exhibit 1.
2. I currently reside at 355 S. Nardo Avenue, Solana Beach, California 92075.
3. I am a co-inventor of the claims of the above-identified patent application. I have reviewed the pending claims. I have also read the Office Action dated January 31, 2002.
4. Results obtained from my laboratory demonstrate that administration of heat shock protein 70i (HSP70i) from an adenoviral vector administered to mouse myocardium *in vivo* protect against ischemic injury.
5. The experiments are described in the following paragraphs. Normal mice (25-30 g) were anesthetized with ketamine/xylazine and placed on a ventilator. A sternotomy was performed at the level of the 2<sup>nd</sup> intercostal space to gain access to the thoracic cavity. The heart

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was exposed and an open stitch of 8-O Ethalon nylon suture was placed at the apex of the left ventricle to allow the heart to be manipulated.

6. Starting at the apex and moving toward the base, five 10  $\mu$ l (50  $\mu$ l total) aliquots of adenovirus ( $10^{10}$  pfu) containing either an empty expression vector (SR-) or HSP70i were injected into the left ventricular free wall using a 0.5 ml insulin syringe with a fixed 29 gauge needle. The adenovirus comprising nucleic acid encoding HSP70i operably linked to the CMV promoter lacked the E1 gene and was replication-deficient. The control adenovirus lacked nucleic acid encoding HSP70i operably linked to the CMV promoter. After injections, the Ethalon suture was removed and the heart repositioned back into the chest cavity. The chest cavity was sutured closed, and a pneumothorax was prevented by using a chest tube to evacuate the air. The animals were removed from the ventilator and allowed to recover for 4 days.

7. At the end of 4 days the animals were sacrificed with an overdose of pentobarbital (10 mg/mouse). Hearts were excised and mounted on a Langendorff perfusion apparatus. A balloon was inserted into the left ventricle through the pulmonary vein and inflated to an end-diastolic pressure of 10 mmHg. The hearts were paced at approximately 400 bpm and the subsequent pressure development recorded using a 2 ft Millar pressure transducer and a computerized data acquisition system. Each heart underwent the following perfusion protocol: 15 minutes aerobic perfusion followed by 20 minutes of global no-flow ischemia, followed by 120 minutes of reperfusion. Function (dp/dt, pressure development) was assessed at the end of the initial 15 min aerobic perfusion and the end of 120 minutes of reperfusion.

8. In mice injected with adenoviral vectors expressing HSP70i, there was a significant improvement ( $p = \text{less than } 0.05$ ) in the maximally developed systolic pressure dp/dt min; the decrease in diastolic pressure dp/dt minutes; and developed pressure. In contrast, no difference in contractile performance was observed in the ischemic hearts before the ischemic periods or in hearts injected with adenoviral vectors not expressing a HSP70i.

9. These results demonstrate that under *in vivo* conditions, increased expression of HSP70i from an adenoviral vector leads to significant protection against ischemic injury as determined by an improvement in contractile performance.

10. Results from additional experiments in the same animal model demonstrated that the release of creatine kinase, which is an indicator of ischemic injury after myocardial infarct in

humans, was significantly decreased in the mouse hearts injected with the adenovirus expressing HSP70i.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application, any patent issuing thereon, or any patent to which this verified statement is directed.

7-3 2002  
Date

W. Dillmann  
Dr. Wolfgang H. DILLMANN



## CURRICULUM VITAE

**WOLFGANG H. DILLMANN, M.D.**  
**Professor of Medicine**

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DATE OF BIRTH:

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PERSONAL DATA:

Married, Luise Steeger  
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EDUCATION AND TRAINING:

1960	Baccalaureate, Gymnasium, Aschaffenburg, Germany
1968	University of Munich, School of Medicine, Germany, Examination in Medicine, Rotating Internship.
1970	M.D., University of Munich, Thesis: Renal Perfusion and Clearance Using Isotope Techniques.
1970 - 1971	Medical Internship, City Hospital Center, Elmhurst, Mt. Sinai Hospital, New York City.
1971 - 1972	Resident, Montefiore Hospital, Albert Einstein College of Medicine, New York.
1972 - 1975	Fellowship Endocrinology and Metabolism, Montefiore Hospital, Albert Einstein College of Medicine, New York.

PROFESSIONAL APPOINTMENTS:

1975 - 1976	Assistant Professor of Medicine Albert Einstein College of Medicine Bronx, New York
1976 - 1978	Assistant Professor of Medicine University of Minnesota
1979 - 1981	Assistant Professor of Medicine University of California, San Diego

1981 - 1987                      Associate of Professor of Medicine  
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1987 - PRESENT                  Professor of Medicine  
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PROFESSIONAL LICENSURE AND CERTIFICATION:

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1977                      American Board of Endocrinology and Metabolism  
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PROFESSIONAL SOCIETIES:

American Thyroid Association; Endocrine Society; American Diabetes Association; Western Society for Clinical Investigation; American Heart Association - Basic Science; American Federation for Clinical Research; American Society for Clinical Investigation; European Thyroid Association; Phi Beta Delta; American Society for Biochemistry & Molecular Biology; Deutsche Gesellschaft fur Endokrinologie; International Society for Heart Research, American Section, Assoc. of American Physicians, Heart Failure Society of America.

RESEARCH SUPPORT:

National Institute of Health  
Merit Award, P.I. W. Dillmann  
CARDIAC ISCHEMIA AND HSP's

National Institute of Health  
R01, P.I. W. Dillmann  
THYROID HORMONE ACTION IN THE HEART

National Institute of Health  
R01, P.I. W. Dillmann  
CARDIAC HYPERTROPHY AND SERCA2 GENE EXPRESSION

National Institute of Health  
R01, P.I. W. Dillmann  
DIABETIC CARDIOMYOPATHY AND CALCIUM FLUX

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Trost SU, Belke DD, Bluhm WF, Meyer M, Swanson E, Dillmann WH:  
Overexpression of the Sarcoplasmic Reticulum Ca<sup>2+</sup> -ATPase Improves  
Myocardial Contractility in Diabetic Cardiomyopathy. *Diabetes* 2002;51:1-6.

## II. INVITED ARTICLES:

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